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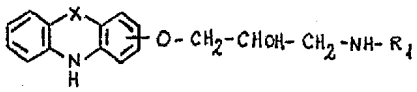
(19)

(54) TRICYCLIC DIPHENYLAMINE DERIVATIVES

(71) We, BOEHRINGER MANNHEIM G.M.B.H., of Mannheim-Waldhof, Federal Republic of Germany, a Body Corporate organised under the laws of the Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new tricyclic diphenylamine derivatives and with the preparation thereof.

The new tricyclic diphenylamine derivatives according to the present invention are compounds of the general formula:—



(I)

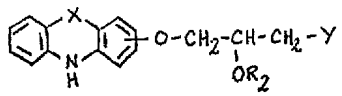
wherein X is a valency bond or a sulphur atom and R_1 is a straight-chained or branched alkyl radical, which can be substituted by a carboxyl group or an alkoxycarbonyl radical; and the pharmaceutically compatible salts thereof.

The alkyl radicals R_1 preferably have a branched chain and can contain 1—8 and preferably 3—5 carbon atoms and the alkyl groups in the alkoxycarbonyl radicals can contain 1—6 and preferably 1—3 carbon atoms.

We have found that the new compounds (I) block the activity of the β-receptors of the sympathetic nervous system and are, therefore, suitable for the treatment and prophylaxis of coronary arterial diseases. Those compounds (I) in which R_1 is a branched alkyl radical, optionally substituted by a carboxyl group or an alkoxycarbonyl radical, are especially effective.

The new compounds of general formula (I) can be prepared, for example, by one of the following methods:—

a) reaction of a compound of the general formula:—



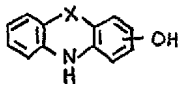
(II)

with a compound of the general formula:—

$$Z—R_3 \qquad \text{(III)}$$

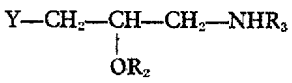
wherein one of the symbols Y and Z is an amino group and the other a reactive residue and R_2 is a hydrogen atom or Y and R_2 together stand for a valency bond, R_3 has the same meaning as R_1 above or is a hydrogen atom and X has the same meaning as above; or

b) reaction of a tricyclic diphenylamine derivative of the general formula:—



(IV)

wherein X has the same meaning as above, with a compound of the general formula:—



(V)

wherein Y, R_2 and R_3 have the same meanings as above, whereafter, if necessary, the radical R_1 is introduced by alkylation and, when R_1 is substituted by a carboxyl group or an alkoxycarbonyl radical, this is converted by saponification, esterification or transesteri-

[P_1

fication and the compound so obtained of general formula (I) is, if desired, converted into a pharmacologically compatible salt.

Reactive residues Y and Z in compounds of general formulae (II) and (III) are, in particular, acid residues, for example of hydrohalic acids and sulphonic acids.

The reactions of compounds of general formula (II) with compounds of general formula (III) according to process a), as well as of compounds of general formula (IV) with compounds of general formula (V) according to process b) are preferably carried out in a polar solvent, for example, in methanol, ethanol or dioxan. The reaction can also be brought about by mixing molar amounts of the reaction components and leaving the mixture to stand at ambient temperature; by brief heating, possibly in a pressure vessel, the reaction can be accelerated.

The reaction of compounds of general formula (IV) with compounds of general formula (V) according to process b) is preferably carried out in the presence of an acid acceptor. However, it is also possible to use alkali metals salts of the hydroxy compounds of general formula (IV).

If a subsequent N-alkylation is to be carried out, i.e. in the case in which R_3 in the starting compounds of general formulae (III) and (V) is a hydrogen atom, it can be carried out, for example, by reaction with reactive alkyl compounds, such as alkyl halides or dialkyl sulphates. The reaction components are preferably heated in an organic solvent, for example in ethanol, in the presence of a base, for example sodium or potassium carbonate. For the preparation of compounds of general formula (I) in which R_1 is a branched alkyl radical, the alkylation of the amino group is preferably carried out by reaction with an appropriate ketone under reducing conditions, catalytic hydrogenation in the presence of Raney nickel or of a platinum metal catalyst preferably being used. The hydrogenation can be carried out in an inert solvent with the use of an excess of the ketone. The alkylation can also be carried out in the presence of an alkali metal borohydride with the use of an excess of the carbonyl compound. The reaction is preferably carried out at ambient temperature or at a slightly elevated temperature.

Saponification of compounds (I), in which R_1 is an alkoxycarbonylalkyl radical, can be carried out with the use of aqueous acids or bases. Esterification of compounds (I), in which R_1 is a carboxyalkyl radical, can be carried out under dehydrating conditions with the use of an excess of an appropriate alcohol, for example, methanol, ethanol, *n*-propanol, isopropanol or *sec.*-butanol. Dehydration of the reaction mixture can be achieved either by azeotropic distillation, using a solvent as entrainer, for example methylene chloride or benzene, or by the addition of a dehydrating substance, for example concentrated sulphuric acid or boron trifluoride etherate. In principle, it is also possible to alkylate the carboxyl group with diazoalkanes. Transesterification of compounds (I), in which R_1 is an alkoxy carbonylalkyl radical, can be carried out by reaction with an excess of an appropriate alcohol.

For the conversion of the compounds of general formula (I) into their pharmacologically compatible salts, they are reacted, preferably in an organic solvent, with an equivalent amount of an inorganic or organic acid, for example hydrochloric acid, hydrobromic acid, phosphoric acid, sulpuric acid, acetic acid, salicylic acid, citric acid, benzoic acid, naphthoic acid, *o*-acetoxybenzoic acid, adipic acid or maleic acid, or, in the case of carboxyl derivatives, they are neutralised with an inorganic or organic base, for example a basic alkali metal or alkaline earth metal compound, ammonia or an organic amine.

The new compounds (I) according to the present invention and the salts thereof can be administered enterally or parenterally in admixture with a liquid or solid pharmaceutical diluent or carrier. As injection medium, water is preferably used which contains the usual additives for injection solutions, such as stabilising agents, solubilising agents and/or buffers. Additives of this kind include, for example, tartrate and citrate buffers, ethanol, complex formers (such as ethylenediaminetetraacetic acid and its non-toxic salts) and high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials which can be used include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly-dispersed silicic acids, higher molecular weight fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycols); compositions suitable for oral administration can, if desired, contain flavouring and sweetening materials.

The following Examples are given for the purpose of illustrating the present invention:—

Example 1

1 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - phenothiazine.

A solution of 5.1 g. 1 - (2,3 - epoxy - propoxy) - phenothiazine in 60 ml. dioxan is mixed with 40 ml. isopropylamine and heated under reflux for 10 hours. Subsequently, the reaction mixture is evaporated and the residue is chromatographed on an aluminium oxide column (200 g. basic aluminium oxide, activity stage IV; eluent methylene chloride). The oily residue obtained after evaporation of the eluted fractions is dissolved in 300 ml. ether and carefully acidified with 2N ethereal hydro-

chloric acid. The precipitated hydrochloride is immediately filtered off with suction and recrystallised several times from methanol/ethyl acetate. There are obtained 4.9 g. (71% of theory) 1 - (3 - isopropylamino - 2 - hydroxy - propoxy) - phenothiazine hydrochloride; m.p. 203°C.

The 1 - (2,3 - epoxy - propoxy) - phenothiazine used as starting material is prepared as follows:

8.5 g. 1 - hydroxy - phenothiazine are dissolved in a mixture of 130 ml. dioxan and 47.5 ml. 1N aqueous sodium hydroxide solution. To this solution are added 31 ml. epichlorhydrin and the reaction mixture then stirred for four hours at 40—45°C. When the reaction is finished, the reaction mixture is diluted with 1 litre water and shaken out four times with 300 ml. amounts of methylene chloride. The methylene chloride phase is dried over anhydrous sodium sulphate and evaporated. For purification, the residue obtained is chromatographed on an aluminium oxide column (200 g. neutral aluminium oxide, activity stage II; eluent benzene). After the evaporation of the fractions and recrystallisation of the residue obtained from ligroin, there are obtained 5.19 g. 1 - (2,3 - epoxy - propoxy) - phenothiazine; m.p. 89—91°C.

Example 2

2 - [2 - Hydroxy - 3 - (phenothiazinyl - 1 - oxy) - propylamino] - propane - 2 - carboxylic acid.

6 g. 1 - (2,3 - epoxy - propoxy) - phenothiazine (prepared analogously to Example 1), together with 2.88 g. of the sodium salt of 2 - aminoisobutyric acid, are heated under reflux in 150 ml. dioxan for 30 hours. The reaction mixture is then evaporated to dryness and the residue is taken up in water, filtered to remove insoluble material and the filtrate is acidified with acetic acid. The precipitate obtained is filtered off and recrystallised several times from dimethyl formamide. There are obtained 3.7 g. (44% of theory) 2 - [2 - hydroxy - 3 - (phenothiazinyl - 1 - oxy) - propylamino] - propane - 2 - carboxylic acid; m.p. 229—230°C.

Example 3

1 - (3 - tert. - Butylamino - 2 - hydroxy - propoxy) - phenothiazine.

11.8 g. 1 - (2,3 - epoxy - propoxy) - phenothiazine are dissolved in 150 ml. ethanol. To this solution are added 35 ml., *tert.*-butylamine and the reaction mixture is heated under reflux for 3 hours. It is then evaporated and the oily residue obtained is chromatographed, for purification, on an aluminium oxide column (300 g. basic aluminium oxide, activity stage III; eluent methylene chloride/benzene=1:1). After evaporation of the eluted fractions, 9.7 g. of an oily residue are obtained. This is dissolved in ether and the solution is acidified with 2N ethereal hydrochloric acid. The precipitate obtained is filtered off and recrystallised from benzene. Yield 11.2 g. (67% of theory) 1 - (3 - *tert.* - butylamino - 2 - hydroxy - propoxy) - phenothiazine hydrochloride; m.p. 118—120°C.

Example 4

2 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - phenothiazine.

A solution of 6.1 g. 2 - (2,3 - epoxy - propoxy) - phenothiazine in 50 ml. dioxan is, after the addition of 50 ml. isopropylamine, heated under reflux for 18 hours. It is then evaporated and the residue obtained is dissolved in methylene chloride and chromatographed over an aluminium oxide column (250 g. basic aluminium oxide, activity stage II, eluent methylene chloride). The residue obtained after the evaporation of the eluted fractions is recrystallised twice from benzene. There are obtained 3.8 g. (51% of theory) 2 - (3 - isopropylamino - 2 - hydroxy - propoxy) - phenothiazine; m.p. 131—132°C.

The 2 - (2,3 - epoxy - propoxy) - phenothiazine used as starting material is prepared as follows:

11.3 g. 2 - hydroxy - phenothiazine are dissolved in a mixture of 150 ml. dioxan and 63.3 ml. 1N aqueous sodium hydroxide solution. After the addition of 41 ml. epichlorhydrin, the reaction mixture is stirred for 5 hours at 35°C. The reaction mixture is then diluted with 1 litre water and shaken out with methylene chloride. The methylene chloride solution is dried over anhydrous sodium sulphate, evaporated and the residue obtained chromatographed on an aluminium oxide column (400 g. neutral aluminium oxide, activity stage II; eluent benzene/methylene chloride=1:1). After evaporation of the fractions, there are obtained 6.1 g. (43% of theory) 2 - (2,3 - epoxy - propoxy) - phenothiazine as an oily residue.

Example 5

3 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - phenothiazine.

A solution of 10.6 g. 3 - (2,3 - epoxy - propoxy) - phenothiazine in 40 ml. dioxan is mixed with 100 ml. isopropylamine and heated under reflux for 25 hours. When the reaction is finished, the reaction mixture is evaporated, the residue obtained is dissolved in methylene chloride and the methylene chloride solution is washed with water. The methylene chloride solution is then dried over anhydrous sodium sulphate and chromatographed over an aluminium oxide column (250 g. basic aluminium oxide, activity stage V; eluent methylene chloride). The fractions are evaporated and the residue obtained is recrystallised several times from methanol. There are obtained 6.9 g. (53% of theory) 3 - (3 - iso-

propylamino - 2 - hydroxy - propoxy) - phenothiazine; m.p. 162—163°C.

The 3 - (2,3 - epoxy - propoxy) - phenothiazine used as starting material is prepared as follows:

12 g. 3 - hydroxy - phenothiazine are dissolved in a mixture of 180 ml. dioxan and 67 ml. 1N aqueous sodium hydroxide solution. To this solution are added 44 ml. epichlorhydrin and the reaction mixture is heated, while stirring under an atmosphere of nitrogen, for 3.5 hours at 45°C. When the reaction is finished, the reaction mixture is mixed with 1 litre water and shaken out 4 times with methylene chloride. The methylene chloride solution is dried over anhydrous sodium sulphate and then evaporated. For purification, the oily residue obtained is chromatographed on an aluminium oxide column (600 g. neutral aluminium oxide, activity stage II, eluent benzene/methylene chloride 1:1). After evaporation of the eluted fractions, 3 - (2,3 - epoxy - propoxy) - phenothiazine remains behind as an oily residue. The yield is 10.6 g. (70% of theory).

Example 6

4 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - phenothiazine.

A solution of 12.5 g. 4 - (2,3 - epoxy - propoxy) - phenothiazine in 90 ml. dioxan is mixed with 90 ml. isopropylamine and heated under reflux for 8 hours. The reaction mixture is then evaporated to dryness and the residue obtained is dissolved in methylene chloride and chromatographed over an aluminium oxide column (550 g. basic aluminium oxide, activity stage IV; eluent benzene/methylene chloride=1:1). After evaporation of the eluted fractions, 5.0 g. of an oil are obtained. This is dissolved in 100 ml. methanol and acidified with a solution of oxalic acid in methanol. After the addition of ethyl acetate and evaporation of the methanol, 3.7 g. of crude crystals are obtained which, after recrystallisation from methanol, give 3.4 g. (20% of theory) 4 - (3 - isopropylamino - 2 - hydroxy - propoxy) - phenothiazine oxalate, melting at 234°C.

The 4 - (2,3 - epoxy - propoxy) - phenothiazine used as starting material is prepared as follows:

A solution of 23 g. 4 - hydroxy - phenothiazine in a mixture of 300 ml. dioxan and 128 ml. 1N aqueous sodium hydroxide solution is, after the addition of 84 ml. epichlorhydrin, stirred for 4 hours at 40°C. under an atmosphere of nitrogen. The reaction mixture is then diluted with 1 litre water and shaken out 4 times with methylene chloride. The methylene chloride phase is dried over anhydrous sodium sulphate, treated with fuller's earth and then evaporated. There are obtained 28 g. 4 - (2,3 - epoxy - propoxy) - phenothiazine in the form of an oil.

Example 7

2 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - carbazole.

To a solution of 14 g. 2 - (2,3 - epoxy - propoxy) - carbazole in 125 ml. dioxan are added 60 ml. isopropylamine and the reaction mixture is heated under reflux for 7 hours. It is then evaporated and the residue obtained is recrystallised several times from methanol. There are obtained 6.8 g. (38% of theory) 2 - (3 - isopropylamino - 2 -hydroxy - propoxy) - carbazole; m.p. 169—171°C.

The 2 - (2,3 - epoxy - propoxy) - carbazole used as starting material is prepared as follows:

A solution of 10 g. 2 - hydroxy - carbazole in a mixture of 60.2 ml. 1N aqueous sodium hydroxide solution and 50 ml. dimethyl sulphoxide is mixed with 45 g. epichlorhydrin. The reaction mixture is stirred for 3 hours at ambient temperature and the precipitated reaction product is filtered off with suction, washed with methylene chloride and dried. There are obtained 14 g. 2 - (2,3 - epoxy - propoxy) - carbazole; m.p. 206—207°C.

Example 8

3 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - carbazole.

10 g. 3 - (2,3 - epoxy - propoxy) - carbazole are dissolved in 80 ml. absolute ethanol. After the addition of 60 ml. isopropylamine, the reaction mixture is heated under reflux for 2 hours. It is then cooled and the precipitated product is filtered off and recrystallised from acetone/alcohol. There are obtained 8.4 g. (67% of theory) of crystalline 3 - (3 - isopropylamino - 2 - hydroxy - propoxy) - carbazole; m.p. 178°C.

The 3 - (2,3 - epoxy - propoxy) - carbazole used as starting material is prepared as follows:

A solution of 16.3 g. 3 - hydroxy - carbazole in a mixture of 190 ml. dioxan and 98 ml. 1N sodium hydroxide is, after the addition of 66 ml. epichlorhydrin, stirred for 2 hours at 40—45°C. The reaction mixture is then diluted with water and shaken out with methylene chloride. The methylene chloride phase is washed with water, dried over anhydrous sodium sulphate and evaporated. There are obtained 16.8 g. 3 - (2,3 - epoxy - propoxy) - carbazole.

Example 9

4 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - carbazole.

A solution of 3.5 g. 4 - (2,3 - epoxy - propoxy) - carbazole in 50 ml. absolute alcohol is mixed with 30 ml. isopropylamine and heated for 3 hours under reflux. When the reaction is finished, the reaction mixture is evaporated to dryness. The residue obtained is taken up in methylene chloride and chromatographed over an aluminium oxide column

(300 g. basic aluminium oxide, activity stage IV; eluent methylene chloride). The eluted fractions are evaporated and the residue is dissolved in methanol and acidified with 2N ethereal hydrochloric acid. The precipitate obtained is filtered off and recrystallised from methanol. There are obtained 3.1 g. (62% of theory) 4 - (3 - isopropylamino - 2 - hydroxy - propoxy) - carbazole hydrochloride; m.p. 234—235°C.

The 4 - (2,3 - epoxy - propoxy) - carbazole used as starting material is prepared in a manner analogous to that described for the preparation of 3 - hydroxy - carbazole in Example 8.

Example 10

Methyl N - [3 - (carbazolyl - 4 - oxy) - 2 - hydroxy - propyl] - α - amino - isobutyrate.

A mixture of 14 g. 4 - (2,3 - epoxy - propoxy) - carbazole and 7 g. methyl α - amino-isobutyrate is heated for 3 hours at 120°C. After cooling, the reaction mixture is taken up with ethyl acetate, diluted with ligroin to twice its volume and filtered with suction. The filtrate is evaporated and the residue obtained is dissolved in ether. By the addition of ethereal hydrochloric acid, the hydrochloride of methyl N - [3 - (Carbazolyl - 4 - oxy) - 2 - hydroxy - propyl] - α - amino - isobutyrate is obtained. The yield is 11 g. (52% of theory).

Example 11

N - [3 - (Carbazolyl - 4 - oxy) - 2 - hydroxy - propyl] - α - aminoisobutyric acid.

6.8 g. 4 - (2,3 - epoxy - propoxy) - carbazole, together with 3.21 g. of the sodium salt of α - amino - isobutyric acid, are heated under reflux for 50 hours in 500 ml. methanol. The reaction mixture is then evaporated, the residue obtained is taken up in 500 ml. water and the aqueous solution is acidified with dilute acetic acid and treated with activated charcoal. After filtration, it is concentrated to 150 ml., the desired product thereby crystallising out. There are obtained 5.4 g. (about 59% of theory) N - [3 - (carbazolyl - 4 - oxy) - 2 - hydroxy - propyl] - α - amino - isobutyric acid which, after recrystallisation from water, has a melting point of 252°C.

Example 12

4 - (3 - tert. - Butylamino - 2 - hydroxy - propoxy) - carbazole.

A solution of 8.3 g. 4 - (2,3 - epoxy - propoxy) - carbazole in 100 ml. absolute alcohol is mixed with 50 ml. *tert.* - butylamine and heated under reflux for 6 hours. When the reaction is finished, the reaction mixture is evaporated to dryness, the residue obtained is dissolved in a mixture of 100 ml. isopropanol and 300 ml. ether and the solution is acidified with an ethereal solution of oxalic acid. The precipitate thus obtained is filtered off and recrystallised from methanol. There are obtained 8.85 g. (about 72% of theory) of crystalline 4 - (3 - *tert.* - butylamino - 2 - hydroxy - propoxy) - carbazole oxalate; m.p. 240—241°C.

Example 13

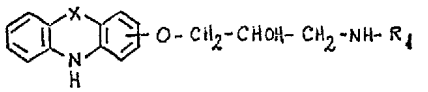
1 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - carbazole.

A solution of 8.2 g. 1 - (2,3 - epoxy - propoxy) - carbazole in 100 ml. absolute alcohol is mixed with 50 ml. isopropylamine and heated under reflux for 2 hours. When the reaction is finished, the reaction mixture is evaporated, the residue is dissolved in isopropanol and the solution obtained is acidified with ethereal hydrochloric acid. The precipitate thus obtained is filtered off and recrystallised from methanol/isopropanol. There are obtained 8.6 g. (75% of theory) of crystalline 1 - (3 - isopropylamino - 2 - hydroxy - propoxy) - carbazole hydrochloride; m.p. 215—216°C.

The 1 - (2,3 - epoxy - propoxy) - carbazole used as starting material is prepared in a manner analogous to that described in Example 8 for the preparation of 3 - (2,3 - epoxy - propoxy) - carbazole.

WHAT WE CLAIM IS:—

1. Tricyclic diphenylamine derivatives of the general formula:—



wherein X is a valency bond or sulphur atom and R_1 is a straight-chained or branched alkyl radical, which can be substituted by a carboxyl group or an alkoxycarbonyl radical; and the pharmacologically compatible salts thereof.

2. 1 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - phenothiazine.

3. 2 - [2 - Hydroxy - 3 - (phenothiazinyl - 1 - oxy) - propylamino] - propane - 2 - carboxylic acid.

4. 1 - (3 - *tert.* - Butylamino - 2 - hydroxy - propoxy) - phenothiazine.

5. 2 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - phenothiazine.

6. 3 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - phenothiazine.

7. 4 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - phenothiazine.

8. 2 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - carbazole.

9. 3 - (3 - Isopropylamino - 2 - hydroxy - propoxy)carbazole.

10. 4 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - carbazole.

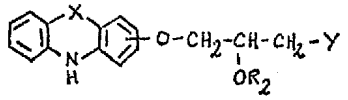
11. Methyl N - [3 - (carbazolyl - 4 - oxy) - 2 - hydroxy - propyl] - α - amino - isobutyrate.

12. N - [3 - (Carbazolyl - 4 - oxy) - 2 - hydroxy - propyl] - α - aminoisobutyric acid.

13. 4 - (3 - *tert.* - Butylamino - 2 - hydroxy - propoxy) - carbazole.

14. 1 - (3 - Isopropylamino - 2 - hydroxy - propoxy) - carbazole.

15. Process for the preparation of tricyclic diphenylamine derivatives of the general formula given in claim 1, wherein a compound of the general formula:—

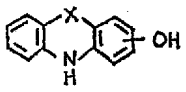


is reacted with a compound of the general formula

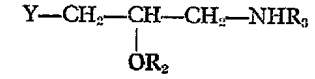
$$Z—R_3$$

in which one of the symbols Y and Z is an amino group and the other one is a reactive residue and R_2 is a hydrogen atom or Y and R_2 together represent a valency bond, R_3 is a hydrogen atom or has the same meaning as R_1 in claim 1 and X has the same meaning as in claim 1, whereafter, when R_3 is a hydrogen atom, the product obtained is alkylated to introduce R_1.

16. Process for the preparation of tricyclic diphenylamine derivatives of the general formula given in claim 1, wherein a tricyclic diphenylamine derivative of the general formula:—



in which X has the same meaning as in claim 1, is reacted with a compound of the general formula:—



in which Y, R_2 and R_3 have the same meanings as in claim 15, whereafter, when R_3 is a hydrogen atom, the product obtained is alkylated to introduce R_1.

17. Process according to claim 15 or 16, wherein the product obtained is esterified, transesterified or saponified.

18. Process according to any of claims 15 to 17, wherein, when the product obtained contains a free carboxylic acid group, it is reacted with a non-toxic inorganic or organic base to give the corresponding salt or when the product obtained does not contain a free carboxylic acid group, it is reacted with a non-toxic inorganic or organic acid to give the corresponding acid-addition salt.

19. Process for the preparation of tricyclic diphenylamine derivatives according to claim 1, substantially as hereinbefore described and exemplified.

20. Tricyclic diphenylamine derivatives according to claim 1, whenever prepared by the process according to any of claims 15 to 19.

21. Pharmaceutical compositions, comprising at least one tricyclic diphenylamine derivative according to claim 1, in admixture with a solid or liquid pharmaceutical diluent or carrier.

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